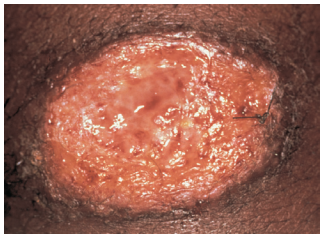

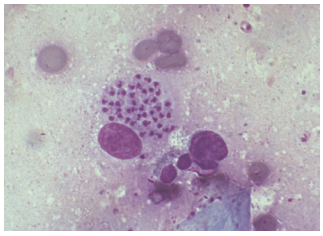

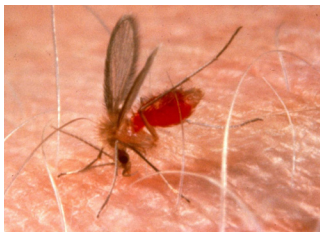

4

Cutaneous Leishmaniasis

Alan J. Magill, Wayne M. Meyers, Ronald C. Neafie, and Mary K. Klassen-Fischer

Introduction

Definition

The cutaneous leishmaniases include a spectrum of self-healing and chronic disease forms caused by protozoan parasites of the genus *Leishmania*. Clinical presentations differ according to parasite burden and host immune response.[1] Although there can be considerable overlap of clinical presentations, 5 distinct cutaneous syndromes are recognized in *Leishmania* infections: 1) simple or localized ulcerative or nodular cutaneous leishmaniasis (CL); 2) mucosal leishmaniasis (ML); 3) leishmaniasis recidivans (LR); 4) diffuse cutaneous leishmaniasis (DCL); and 5) post-kala-azar dermal leishmaniasis (PKDL). Immunocompromised patients may have atypical presentations.[2]

Oligoparasitic (low parasite burden) syndromes are chronic, persistent infections that follow primary ulcerative disease (ML and LR) or drug therapy for kala-azar (early forms of PKDL). Polyparasitic syndromes such as ulcerative and nodular CL, DCL, and late or nodular PKDL are characterized by a high parasite burden.

Synonyms

The ulcers, nodules, and other cutaneous lesions caused by *Leishmania* sp are known around the world by a variety of descriptive or geographic terms. Cutaneous leishmaniasis (CL) has many colorful names, such as Aleppo sore, Baghdad boil, bouton d'orient, chiclero ulcer, Delhi boil, oriental sore, pian-bois, Sart sore, and uta. Mucosal leishmaniasis (ML) is also called mucocutaneous leishmaniasis and espundia. Leishmaniasis recidivans (LR) is known as chronic leishmaniasis or lupoid leishmaniasis. Diffuse cutaneous leishmaniasis (DCL) is sometimes referred to as disseminated cutaneous leishmaniasis, although disseminated CL is usually reserved for a syndrome described in Brazil.[3]

General Considerations

In 1903, Wright described the leishmania parasite that causes CL.[4] He outlined the morphology of amastigotes found in the facial lesion of a young Armenian immigrant to the United States. Borovsky, a Russian bacteriologist, had given the first description of the parasite in an ulcerative lesion in 1898, but his report was not translated into English until 1938.[5,6] In 1908, Nicolle isolated the parasite in in-vitro culture from typical cutaneous lesions.[7] His description of the flagellate promastigote form of the parasite established the similarity of the leishmanias of CL and kala-azar. Carini, working in Brazil, first described leishmania parasites in palatal lesions in a patient with ML in 1911.[8] In Venezuela in 1948, Convit and Lapenta reported the first case of DCL.[9]

Leishmania sp traditionally carried markers related to clinical syndrome and geographic distribution (*Leishmania*

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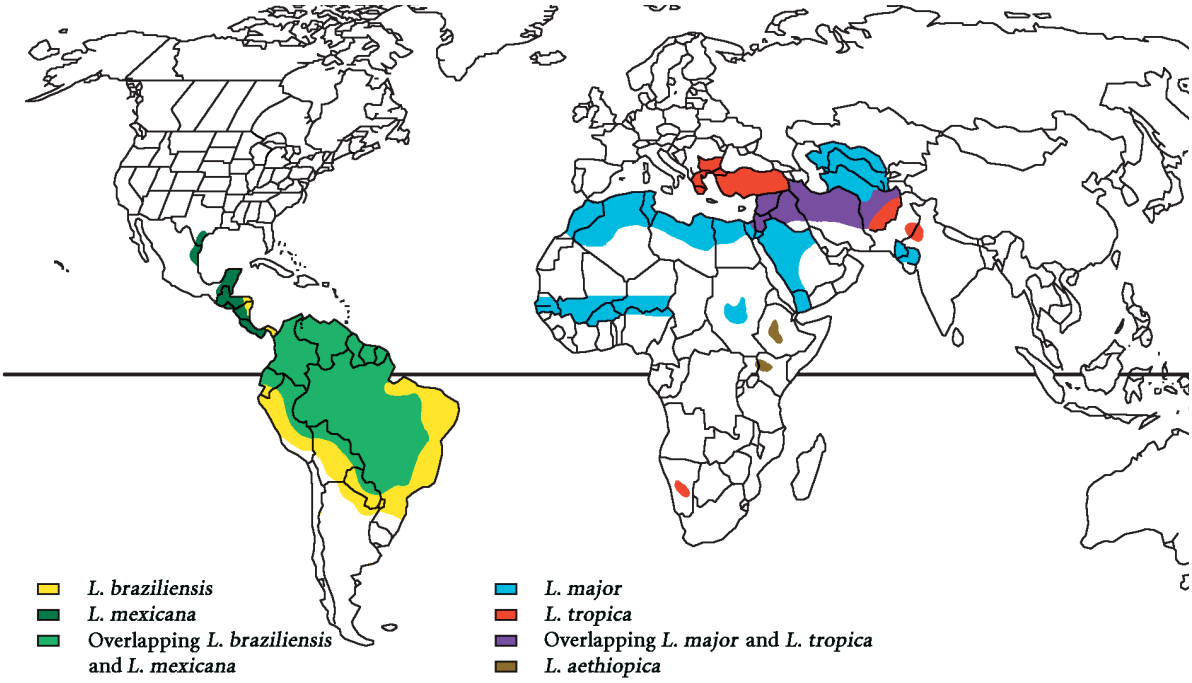

Figure 4.1
Geographical distribution of *Leishmania* sp

braziliensis as the cause of ML in the New World (Western); *Leishmania tropica* and *Leishmania major* as the cause of CL in the Old World (Eastern). However, beginning in the 1970s, descriptors such as biologic, immunologic, and biochemical characteristics of the parasite significantly changed the classification of leishmaniases. Isozyme electrophoresis has shown that no single *Leishmania* sp is uniquely associated with a clinical syndrome.[10] For example, *Leishmania amazonensis* has been isolated from individuals with ML, CL, DCL, and kala-azar in Brazil.[11] *Leishmania guyanensis* and *Leishmania panamensis* have been isolated from individuals with ML.[12,13] In the Old World, *L. tropica*, a particularly heterogeneous group of parasites,[14] has been isolated from individuals with kala-azar,[15-17] viscerotropic leishmaniasis,[18,19] febrile systemic illness,[20] and isolated lymphadenopathy. Diffuse cutaneous leishmaniasis is associated with parasites of the *Leishmania mexicana* complex in the New World and *Leishmania aethiopica* in the Old world. LR is most commonly associated with *L. tropica*. Post-kala-azar dermal leishmaniasis (PKDL) is seen with the *Leishmania donovani* complex, and ML with the *L. braziliensis* complex. Cutaneous leishmaniasis can be caused by any of the leishmanias.

Epidemiology

Worldwide prevalence and annual incidence of the cutaneous leishmaniases are unknown with any certainty. The study of Ashford et al suggests that there are approximately 300,000 cases per year from a population of 200 million at risk.[21] Actual prevalence is probably higher because estimates in many countries are obtained by passive notification, not by active surveillance.[22] In endemic areas, small, minimally symptomatic lesions are frequently ignored or treated with traditional therapies such as burning with a hot iron or applying battery acid. When it is available, drug therapy at local clinics can be prohibitively expensive or not available, thus people with CL often do not seek treatment.

Excellent reviews of the geographic distribution of the cutaneous leishmaniases in the New World[23,24] and Old World[25] have been published. The cutaneous leishmaniases are endemic in 82 countries (Fig 4.1).[26] Cutaneous leishmaniasis is widely distributed in the Americas from southern Texas to northern Argentina. ML is most common in the jungles of Amazonia (especially in southern Brazil), but cases have been reported throughout the Americas. Most patients with DCL come from Brazil, the Dominican Republic, Ethiopia and Venezuela, but there are sporadic infections in Bolivia, Colombia, Honduras, Mexico, Peru, Kenya, and southern United States. Leishmaniasis recidivans (LR) is most common in the Middle East. PKDL is seen in India and East Africa (Kenya and the Sudan) following treatment of kala-azar with pentavalent antimony (SbV).

Residents of endemic areas with enzootic cycles between infected sandflies and nonhuman mammalian reservoir hosts are likely to be infected at an early age. Epidemics of

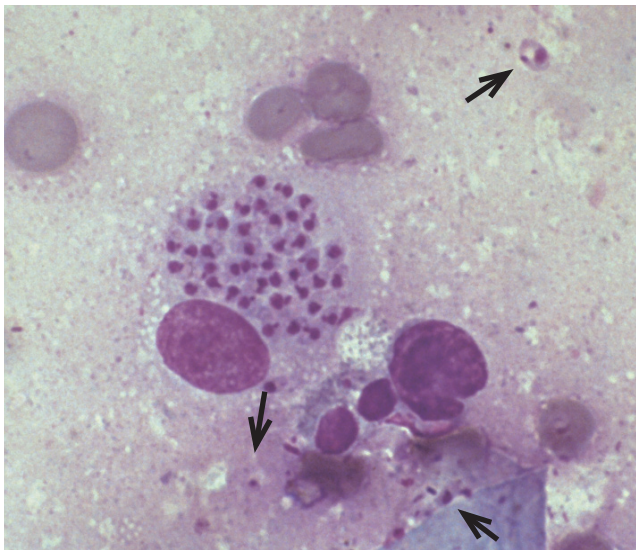

Figure 4.2
Smear of skin lesion demonstrating amastigotes within macrophage. Note also a few extracellular organisms (arrows). Giemsa x750

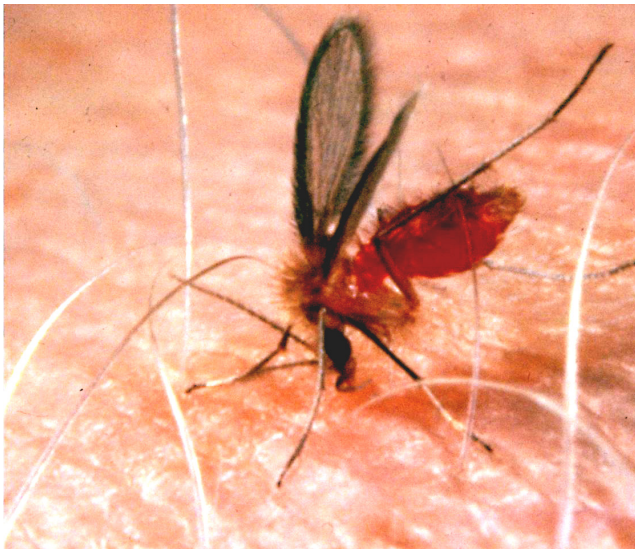

Figure 4.3
Female sandfly (*Lutzomyia longipalpis*) taking blood meal from human skin. Except for "V" position of wings over thorax, sandflies assume mosquito-like position while biting. Note erythema around bite site and sandfly's hairy body and wings.

CL frequently occur when a nonimmune population intrudes into a natural enzootic cycle. The population at highest risk for CL is nonimmune expatriates such as tourists, soldiers, new settlers, and construction or agricultural workers.[27,28] New development, construction, or agricultural projects and military operations are commonly accompanied by outbreaks. Socioeconomic factors, population growth, and migration also influence the epidemiology of CL.[29,30]

Infectious Agent

Morphologic Description

In human tissue, leishmanial parasites are in the amastigote form and multiply within histiocytes. Amastigotes are ovoid or round and 1.5 µm to 3 µm in diameter (Fig 4.2). They have a thin cell membrane, a relatively large nucleus, and a rod-shaped kinetoplast that is not always visible in tissue sections because of its orientation within the parasite.

Life Cycle and Transmission

Promastigotes of *Leishmania* sp are motile and elongate, with a flagellum at the anterior end. Metacyclic promastigotes, the infective form of the parasite, are carried in the salivary glands of female sandflies (*Phlebotomus* sp in the Old World; *Lutzomyia* sp (Fig 4.3) and *Psychodopygus* sp in the New World) and transmitted to a host during a blood meal (Fig 4.4). Promastigotes attach to mononuclear phagocytes and enter host endosomes, which then fuse with lysosomes. Promastigotes transform into nonmotile, oval amastigotes with no free flagellum. Amastigotes persist and replicate by binary fission within the parasitophorous vacuole. The expanding vacuole nearly fills the cell, leading to lysis and cell death. Released daughter amastigotes attach to and penetrate other cells. When a sandfly ingests an infected cell, amastigotes transform into promastigotes, which live and develop extracellularly in the fly's alimentary tract and then migrate to the salivary glands.

Rarely, transmission is congenital, sexual, occupational, or bloodborne through transfusion or IV drug use.[31-34]

Clinical Features and Pathogenesis

The typical lesion of ulcerative CL starts as a small, erythematous papule at the site where promastigotes are inoculated.[35] The incubation period is usually several weeks to months, but can be a few days or years. In most cases, within a few weeks the papule enlarges, crusts over, and breaks down into a slow-growing ulcer that may be several centimeters in diameter (Fig 4.5). As the ulcer grows, patients develop a delayed hypersensitivity (DH) reaction to leishmanial antigens. The ulcer is shallow and well-defined, with a raised erythematous border and central granulation tissue (Fig 4.6) Very rigorous cleaning and debridement is necessary to get to a clean ulcer base (Fig 4.7). Surrounding inflammation may be minimal or quite marked. The ulcer heals slowly, leaving a depressed, atrophic scar. Nodular presentations of cutaneous leishmaniases are not uncommon (Fig 4.8), Sporotrichoid presentations (Fig 4.9a) and satellite lesions (Fig 4.9b) are common. Hyperkeratotic lesions do not ulcerate. Lymph nodes proximal to lesions

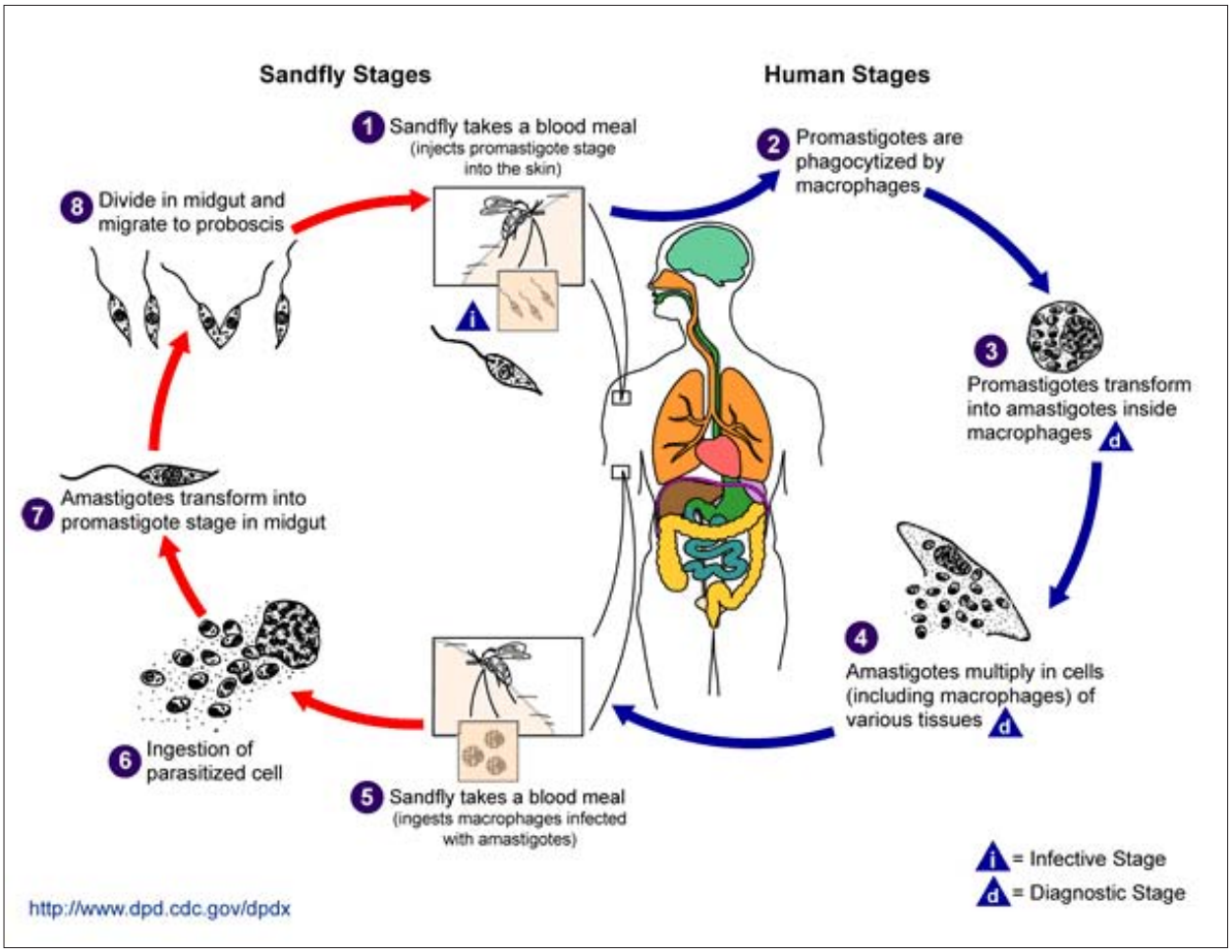

Figure 4.4
Life cycle of *Leishmania* sp in humans. Promastigotes enter skin as infected sandfly takes blood meal. Promastigotes transform into amastigotes that reproduce by binary fission in histiocytes. Ruptured histiocytes release amastigotes, which invade other histiocytes that are eventually ingested by a sandfly, repeating the cycle.

may be involved. Macules, papules, plaques (Figs 4.10 to 4.12), nodules (Fig 4.13), and psoriasiform, varicelliform, eczematous, and keloidal (Fig 4.14) lesions are uncommon, but have been reported. Lesions heal by scarring (Fig 4.15).

Mucosal leishmaniasis (ML) is a chronic, oligoparasitic syndrome associated with persistent and enhanced DH reaction to leishmanial antigens. This syndrome develops in up to 5% of individuals following primary ulcerative CL and is almost exclusively associated with *L. braziliensis* infection in the New World. Mucosal leishmaniasis is characterized by metastatic involvement of oro- and nasopharyngeal tissue following a primary ulcerative lesion. Patients may initially experience nosebleed, nasal congestion, and mucopurulent expectoration. Mucosal leishmaniasis progresses slowly over many years, destroying tissues of the nose, palate, uvula, and hypopharynx. Gross changes include septal perforations, irregular vegetative growths, and swelling (Fig 4.16). Crusted, vegetative, heavily infiltrated lessions may involve mucocutanous areas (Fig. 4.17) Leishmaniasis may rarely involve the perineum and adjacent areas (Fig 4.18). Late-stage ML is often accompanied by persistent cough and hoarseness. Extensive tissue destruction can compromise the respiratory tract and lead to pulmonary infections.

Leishmaniasis recidivans (LR) is also a chronic, oligoparasitic syndrome associated with persistent and enhanced DH reaction to leishmanial antigens. It is characterized by painless, recrudescing, brownish-red, lupoid nodules around the periphery of healed primary lesions (Fig 4.19). Leishmaniasis recidivans is most commonly associated with *L. tropica* infection and is seen in the Middle East.

Diffuse cutaneous leishmaniasis (DCL), an uncommon syndrome, is a chronic, polyparasitic syndrome associated with anergy to leishmanial antigen. It is characterized by disseminated nodules which are often prominent about the

head and neck (Figs 4.20 to 4.22a). Because of their gross clinical similarities, DCL and lepromatous leprosy are frequently mistaken for each other. Diffuse cutaneous leishmaniasis, however, lacks many of the cardinal features of lepromatous leprosy, such as madarosis (loss of eyelashes or brows), sensory changes, and changes of the major peripheral nerves. Furthermore, the nodules of lepromatous leprosy are usually firmer than those of DCL.

Post-kala-azar dermal leishmaniasis (PKDL) is a spectrum of dermatologic lesions, including macules, papules, and nodules, that develops during or following treatment of Indian or African kala-azar with SbV (Figs 4.22b & 4.22c) PKDL.[36,37] The initial lesions may resolve spontaneously over a few weeks or months, or develop into chronic papulonodular lesions with heavy parasite burdens. A patient with chronic lesions is a likely reservoir for anthroponotic (human-sand-fly-human) transmission.

Asymptomatic patients with latent infection can develop localized cutaneous lesions at the site of blunt, penetrating, or surgical trauma.[38,39] Immunosuppressed patients may develop disseminated cutaneous lesions.[13,40]

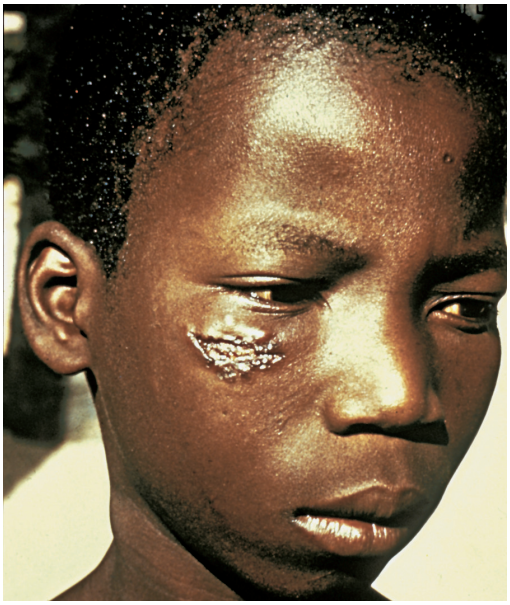

Figure 4.5
Chronic ulcer of cutaneous leishmaniasis (CL) in Nigerian boy. Ulcer is shallow with raised edges.

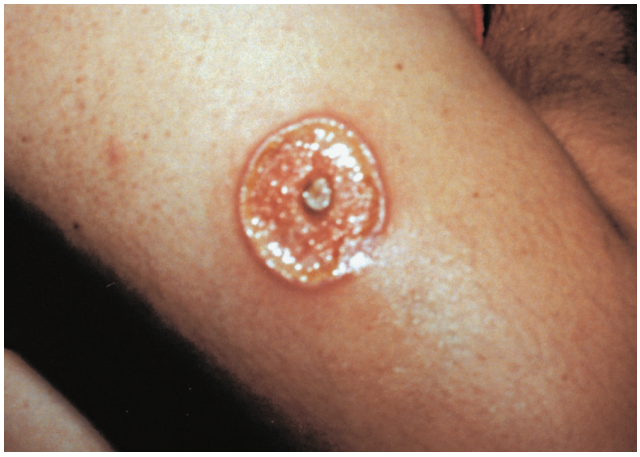

Figure 4.6
Early shallow ulcer of cutaneous leishmaniasis (CL) (4.5 cm in diameter) with raised edges and granulating center.

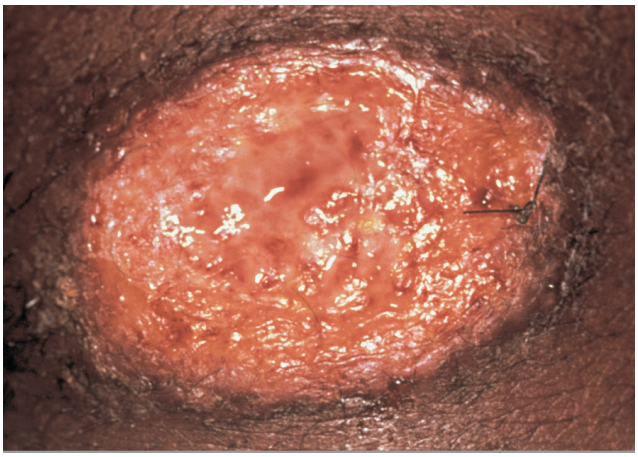

Figure 4.7
Shallow ulcer of cutaneous leishmaniasis (CL), 4.5 cm in diameter, with central granulation tissue and raised edges. Most likely this lesion had a crusty exudate on initial presentation.

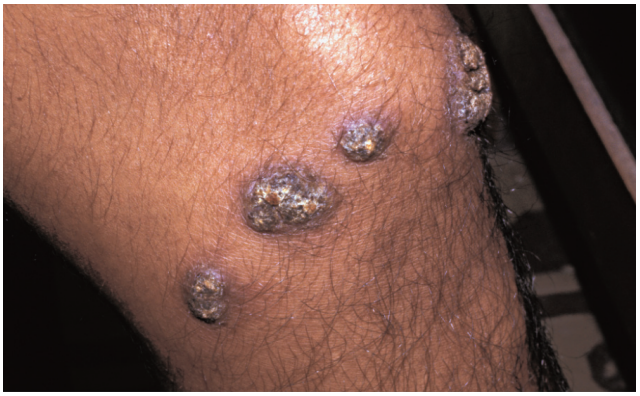

Figure 4.8
Nodular, non-ulcerative presentation of cutaneous leishmaniasis (CL).

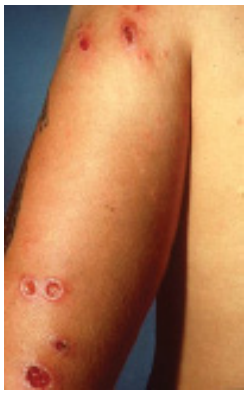

Figure 4.9a
Sporotrichoid presentation of cutaneous leishmaniasis (CL).

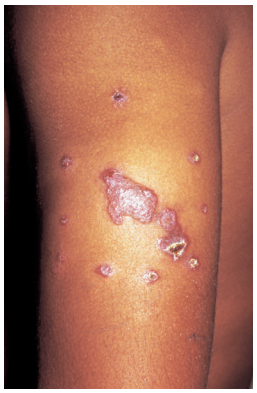

Figure 4.9b
Lesions of cutaneous leishmaniasis (CL) with multiple satellite papules on arm of Brazilian patient.

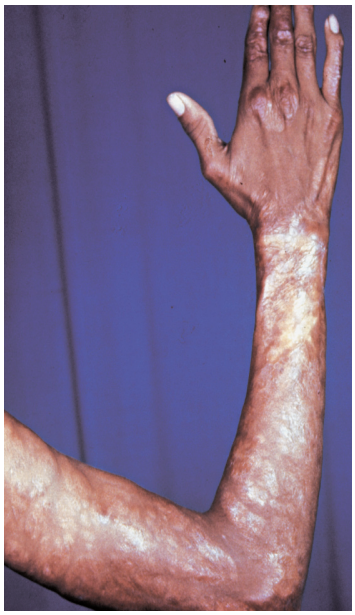

Figure 4.10
Plaques of cutaneous leishmaniasis cover nearly entire arm of Brazilian

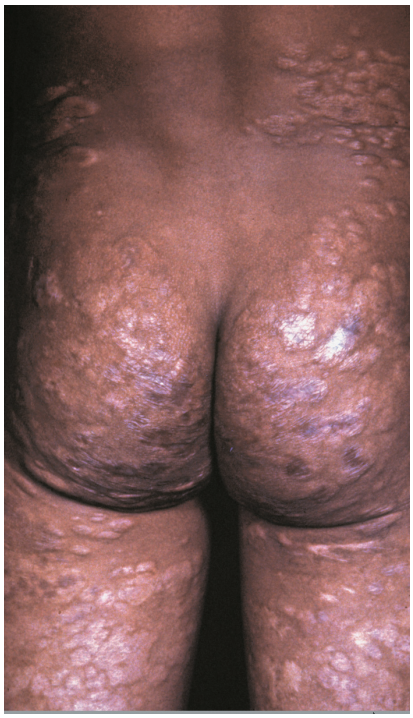

Figure 4.11
Same patient as Figure 4.10, showing widespread papules and plaques of cutaneous leishmaniasis.

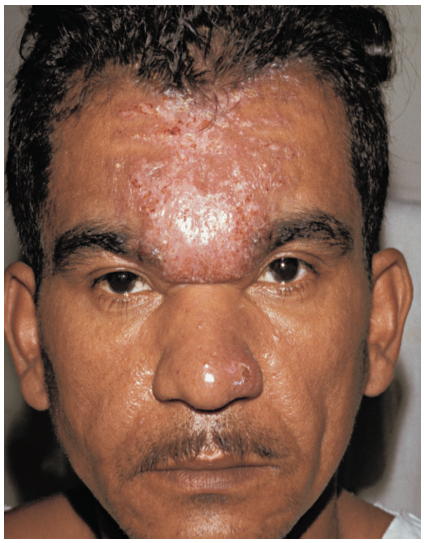

Figure 4.12
Maculopapular cutaneous leishmaniasis on forehead of Brazilian patient.

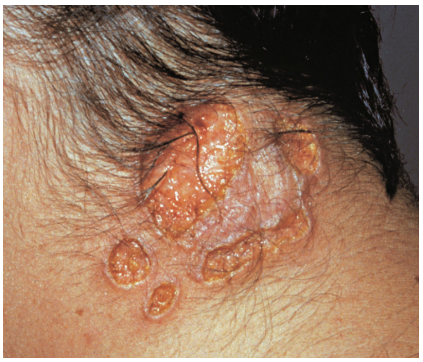

Figure 4.13
Ulcerated nodules of cutaneous leishmaniasis on nape of Brazilian patient.

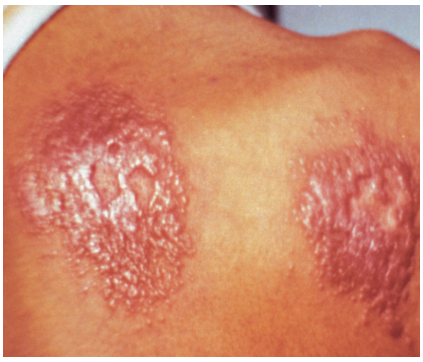

Figure 4.14
Yemenite patient with plaques of cutaneous leishmaniasis containing keloids.

Pathologic Features

In early CL, epidermal changes include hyperkeratosis, basal cell degeneration, and epidermal hyperplasia, and may also consist of parakeratosis, pseudoepitheliomatous hyperplasia, follicular plugging, epidermal atrophy, acanthosis, and intraepidermal abscesses (Figs 4.23 to 4.26). In the dermis, where the inflammatory infiltrate consists of histiocytes, lymphocytes, and plasma cells (Fig 4.27), many intra- and extracellular amastigotes may be observed (Figs 4.28 to 4.31). As CL progresses, the epidermis becomes increasingly hyperplastic and ulcerates (Fig 4.32). The dermis becomes necrotic and infiltrated by increasing numbers of vacuolated histiocytes, epithelioid cells,

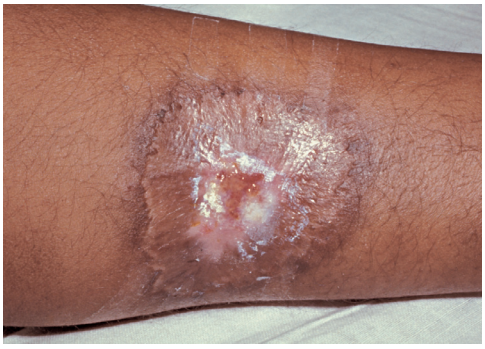

Figure 4.15
Nearly healed cutaneous leishmaniasis (CL) on calf of Brazilian patient.

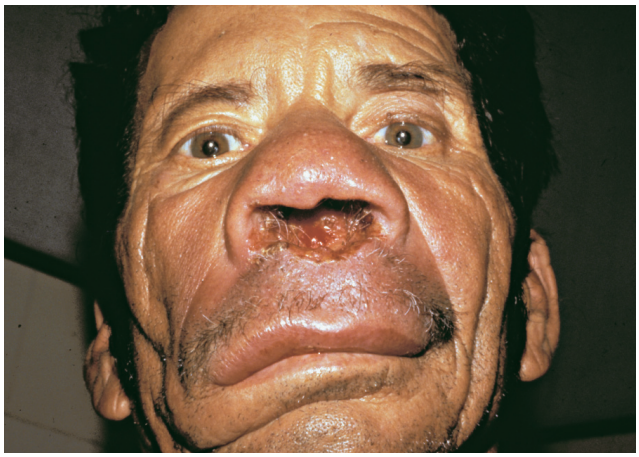

Figure 4.16
Brazilian patient with mucosal leishmaniasis (ML) (espundia) showing ulceration of nasal septum.

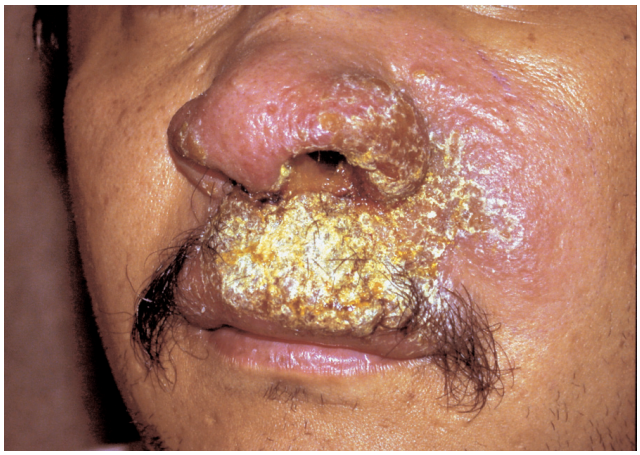

Figure 4.17
Mucocutaneous leishmaniasis in Honduran patient. Note crusted, vegetative, and heavily infiltrated lession.

lymphocytes, plasma cells, and giant cells (Figs 4.33 to 4.35). There may be neutrophils in the ulcer bed. As necrotizing (Fig 4.36) or nonnecrotizing (Figs 4.37 to 4.39) granulomas develop, amastigotes decline in number and may be extremely difficult to find.[41] In such instances, biopsies should be taken from the periphery of the ulcer, including the nonulcerated edge. As healing takes place, granulation tissue and fibrosis fill the ulcer crater. Satellite lesions that develop along the course of draining lymphatic channels can cause necrotizing granulomas or histiocytic infiltration in lymph nodes (Figs 4.40 to 4.43).[42]

Mucosal leishmaniasis is characterized by chronic inflammation, necrotizing granulomas, and occasional ulceration (Fig 4.44). The inflammatory infiltrate is made up of numerous lymphocytes, epithelioid cells, and giant cells (Fig 4.45). Early in ML, parasites may be abundant; in chronic ML, they are rarely seen (Fig 4.46).

The histologic features of LR are similar to those of acute and chronic CL. Macrophages, lymphocytes, and plasma cells infiltrate the dermis, and necrotizing granulomas with epithelioid cells develop. Amastigotes vary in number and are usually very difficult to find. Healing is accompanied by fibrosis.

In DCL, numerous macrophages containing multiple amastigotes infiltrate the dermis (Fig 4.47). Although there may be a few lymphocytes and plasma cells, there is usually no necrosis or granuloma formation. The epidermis is atrophic but not ulcerated (Fig 4.48). A clear zone beneath the basal layer of the epidermis is free of inflammatory cells (Fig 4.49).

Histologic features of PKDL often resemble those of DCL. In macular lesions, histiocytes, lymphoid cells, and plasma cells infiltrate the upper dermis and amastigotes are rare. In plaque lesions, the infiltration is denser, consisting of histiocytes, lymphoid cells, and especially plasma cells,

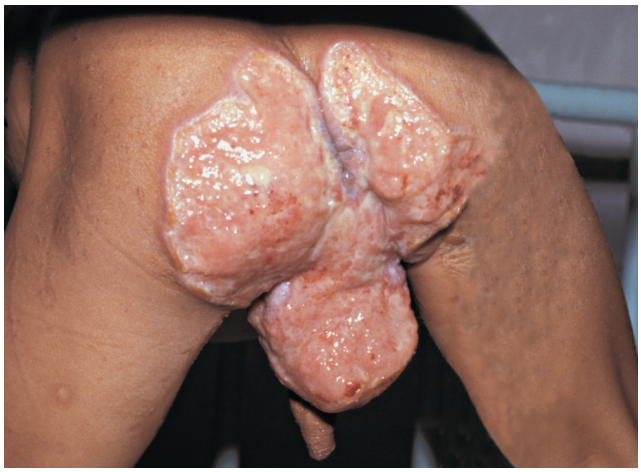

Figure 4.18
Brazilian mucocutaneous leishmaniasis patient with rare involvement of perineum and adjacent areas.

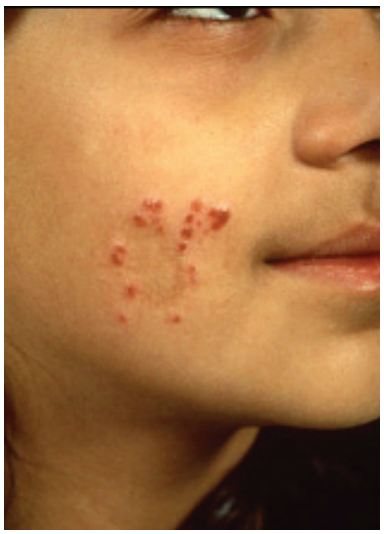

Figure 4.19
Leishmaniasis recidivans, usually associated with *Leishmania tropica*. Note lupoid satellite nodules.

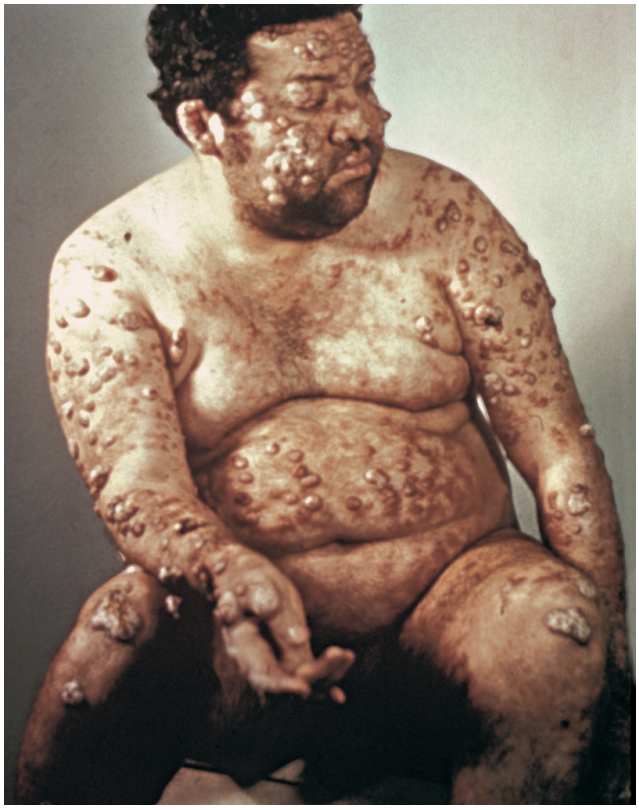

Figure 4.20
Diffuse cutaneous leishmaniasis (DCL) in Venezuelan patient. Clinically, widespread nodules may be mistaken for lepromatous leprosy or cutaneous lymphoma. Madarosis, typical of advanced lepromatous leprosy, is absent.

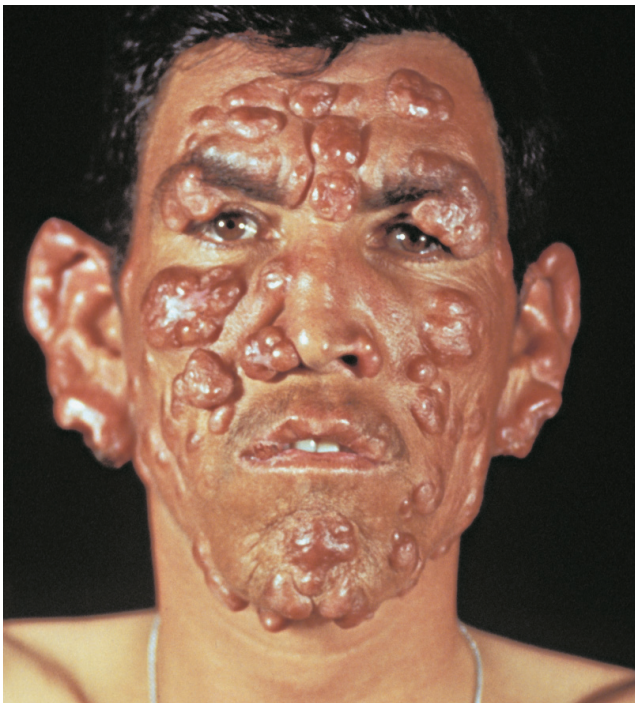

Figure 4.21
Diffuse cutaneous leishmaniasis (DCL) in 24-year-old Mexican patient. Nodules and diffuse infiltrations do not selectively involve central portions of face, as in lepromatous leprosy.

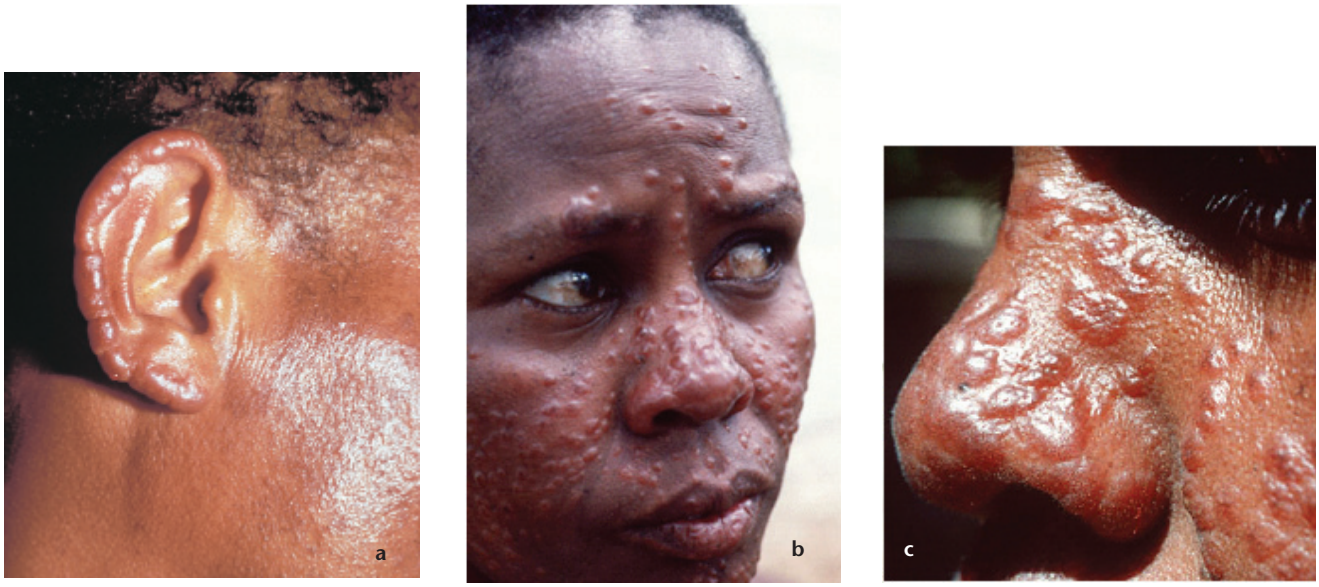

Figure 4.22
a. Diffuse cutaneous leishmaniasis (DCL) of pinna, frequently confused with leprosy. b and c. Infiltration and nodules of post-kala-azar dermal leishmaniasis (PKDL) forming a butterfly pattern on face that can become generalized.

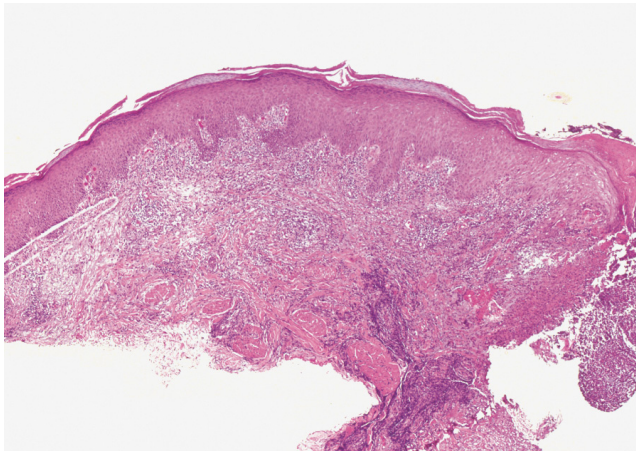

Figure 4.23
Ulcer of cutaneous leishmaniasis (CL) in soldier returned from Operation Desert Storm in Middle East, showing inflammation and necrosis. Note epidermal hyperplasia. See also Figure 4.30. x24

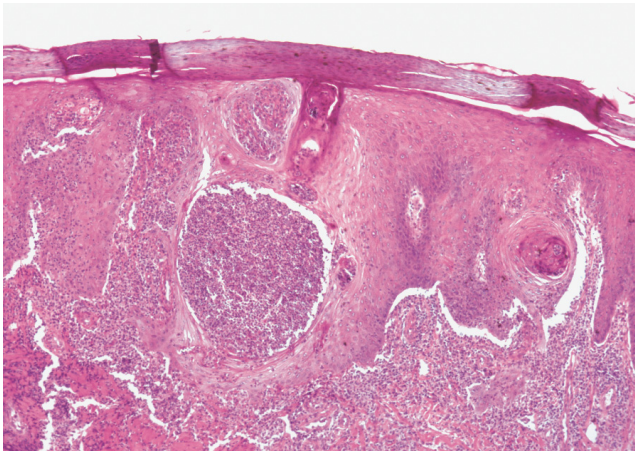

Figure 4.24
Early cutaneous leishmaniasis in same patient as Figure 4.26, showing hyperkeratosis, epidermal hyperplasia, and inflammation. x45

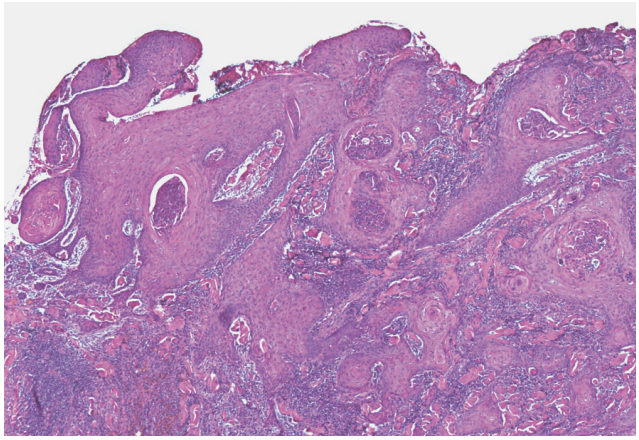

Figure 4.25
Cutaneous leishmaniasis in 51-year-old Cuban patient with nonhealing ulcer at site of sandfly bite on leg. Biopsy shows pseudoepitheliomatous hyperplasia and intraepidermal abscess. See also Figures 4.39, 4.51, 4.53, and 4.54. x24

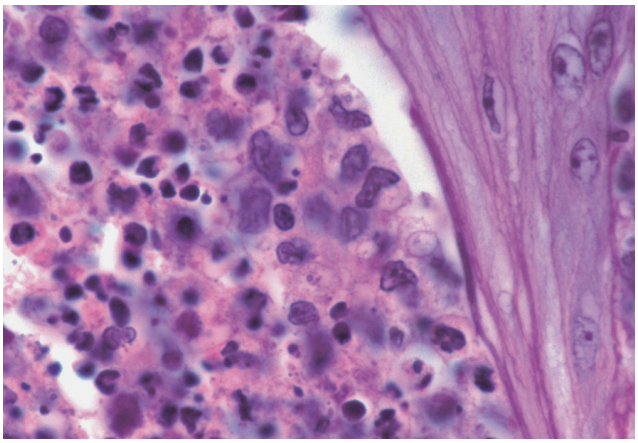

Figure 4.26
Higher magnification of intraepidermal abscess in patient described in Figure 4.24. x685

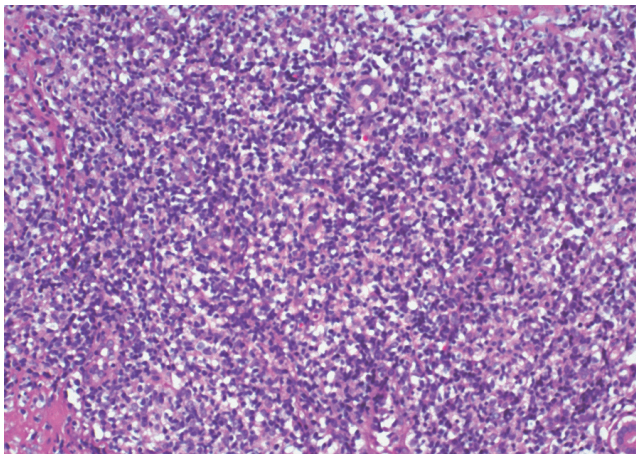

Figure 4.27
Dermal infiltration of histiocytes, lymphocytes, and plasma cells in cutaneous leishmaniasis. x125

and amastigotes are more frequent than in macular lesions. In nodular lesions, cellular exudates extend into the subcutis and intracellular amastigotes are usually abundant.

Diagnosis

The different parasitologic techniques for confirming *Leishmania* infection are variously effective, depending on whether the syndrome under examination is oligoparasitic or polyparasitic. A confirmed parasitologic diagnosis is established by any of the following methods:

1) **Visualization of amastigotes in Giemsa-stained smears, aspirates, or histologic sections.** Polyparasitic syndromes such as early-stage CL, DCL, and papulonodular forms of PKDL are easily confirmed with Giemsa-stained smears (Fig 4.2). Oligoparasitic syndromes such as ML, LR, macular PKDL, and late-stage (healing) CL are more

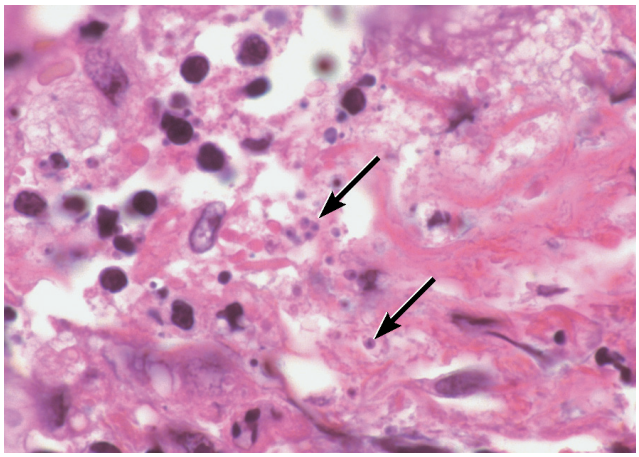

Figure 4.28
Biopsy from area near ulcerated epidermis shows several amastigotes (arrows) in dermis. See also Figures 4.32, 4.33, and 4.36. x655

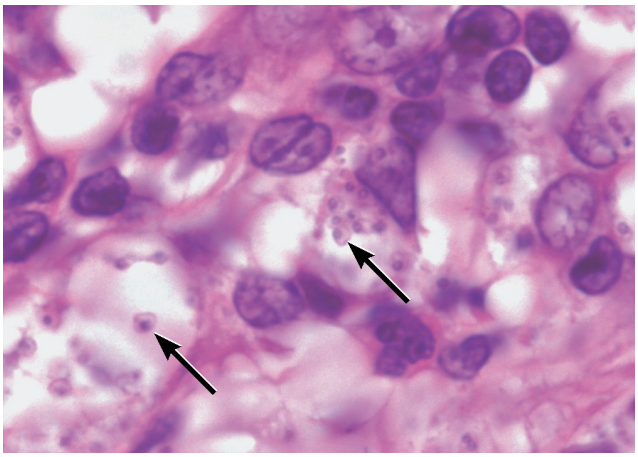

Figure 4.29
Multiple amastigotes (arrows) in 44-year-old patient from Dominican Republic. Patient developed multiple skin nodules starting at age 12. See also Figure 4.55. x945

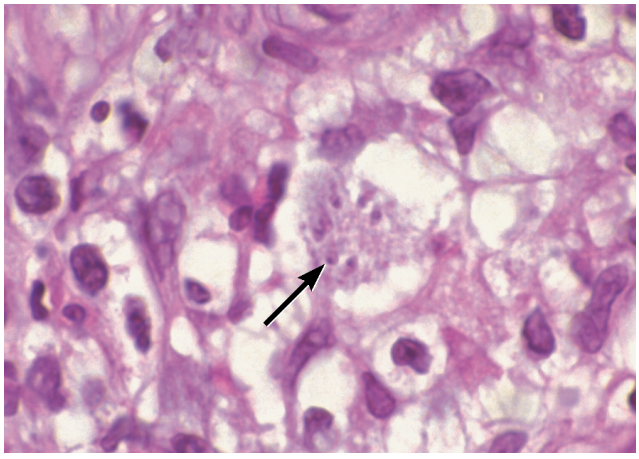

Figure 4.30
Amastigotes (arrow) in specimen shown in Figure 4.23. x960

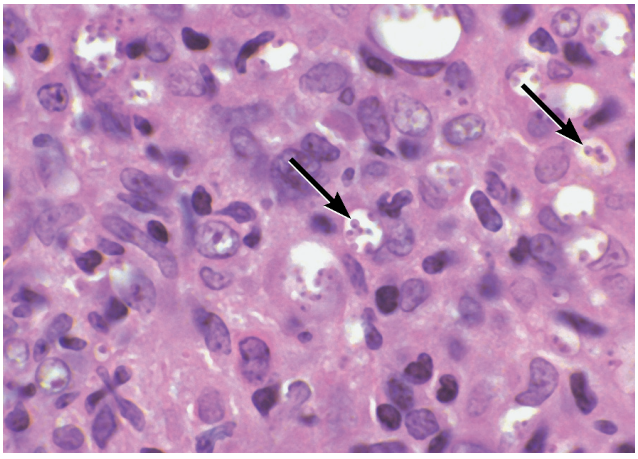

Figure 4.31
Amastigotes (arrows) within histiocytes. See also Figure 4.35. x600

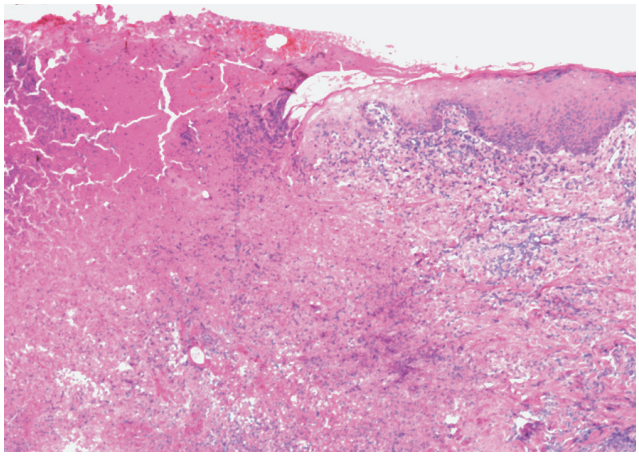

Figure 4.32
Ulceration in cutaneous leishmaniasis. Same specimen as Figure 4.28. See also Figures 4.33 and 4.36. x50

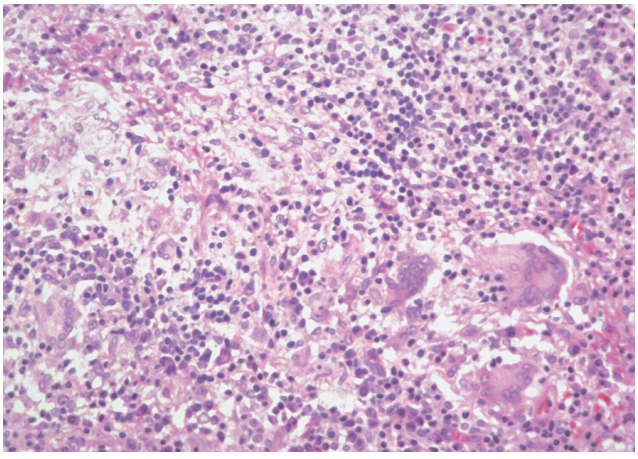

Figure 4.33
Later biopsy from same patient as Figure 4.28 showing necrosis and infiltration of dermis by mixed inflammatory cells, including multinucleated giant cells. No amastigotes were found. See also Figures 4.32 and 4.36. x175

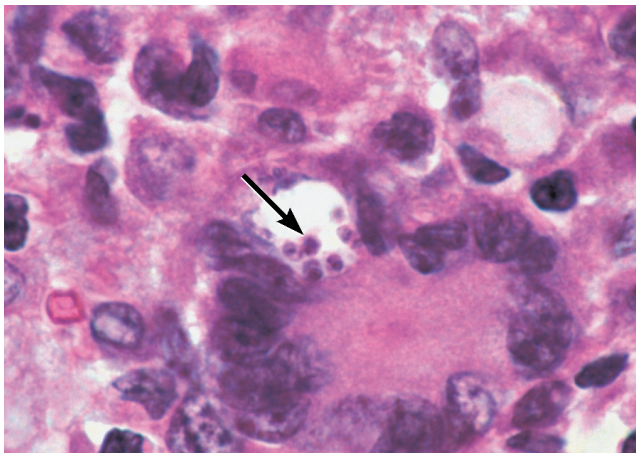

Figure 4.34
Multinucleated giant cell containing multiple amastigotes (arrow). Ethiopian patient had large facial lesion involving forehead, eyebrow, nose, and malar area. Three smears and leishmanial cultures were negative. x1115

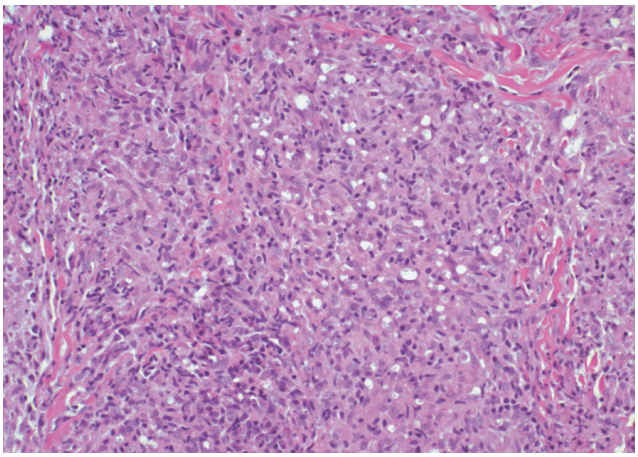

Figure 4.35
Diffuse histiocytic infiltration of dermis in cutaneous leishmaniasis . Same patient as Figure 4.31. x120

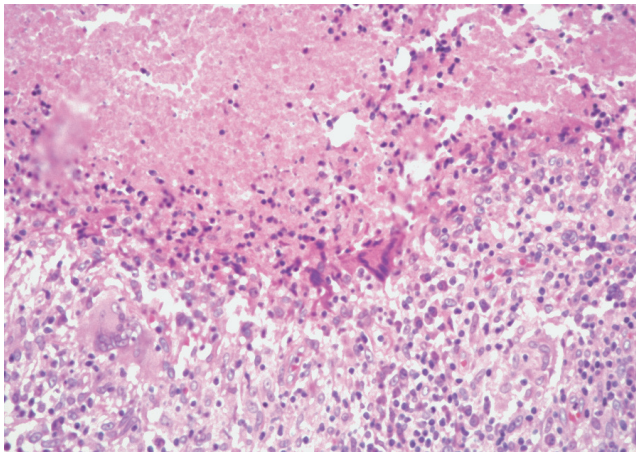

Figure 4.36
Necrobiotic granuloma in deep dermis. No amastigotes were found. Same specimen as Figure 4.33. See also Figures 4.28 and 4.32. x170

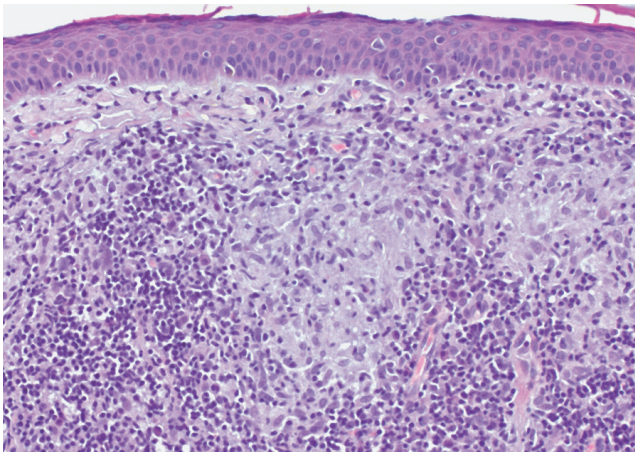

Figure 4.37
Noncaseating granulomas in 26-year-old soldier with cutaneous leishmaniasis who had traveled to Panama, Honduras, and Kuwait. For 3 years, patient had slow-growing papule on forehead that was unresponsive to topical steroids. See also Figure 4.38. x120

difficult or sometimes impossible to confirm with standard Giemsa-stained smears. Because factors such as specimen quality, staining methods, and the skill of the microscopist can dramatically affect the sensitivity of this diagnostic procedure, a negative smear does not necessarily exclude a diagnosis of leishmaniasis. In histologic sections, amastigotes stain well with H&E (Fig 4.50) or Brown-Hopps modified tissue gram stain (Figs 4.51 & 4.52). In our experience, the Brown-Hopps stain creates the least amount of background staining and the strongest contrast from surrounding tissue, which makes identifying amastigotes much easier.[43] Other stains sometimes used to identify amastigotes in tissue, including Giemsa (Fig 4.53), Wilder's reticulum (Fig 4.54), PAS (Fig 4.55), and immunoperoxidase (Fig 4.56) stains, offer no advantage over the Brown-Hopps

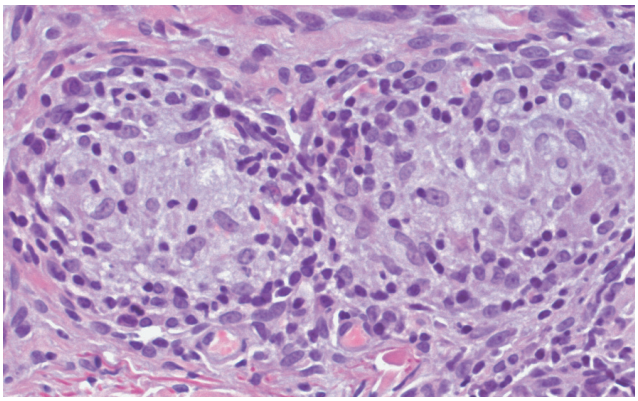

Figure 4.38
Two delayed hypersensitivity granulomas in specimen shown in Figure 4.37. x245

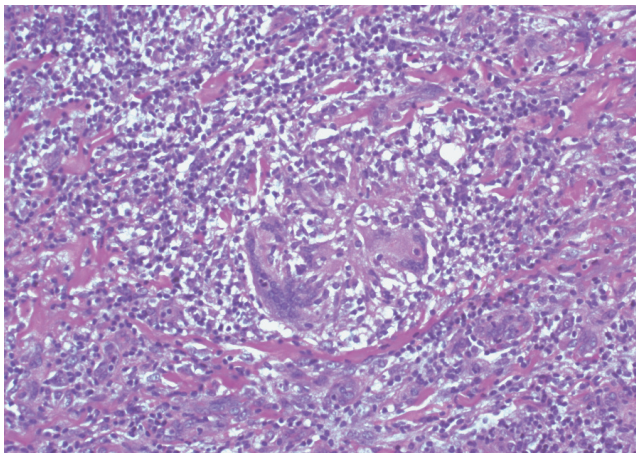

Figure 4.39
Granulomatous area of dermis in specimen shown in Figure 4.25. See also Figures 4.51, 4.53, and 4.54. x115

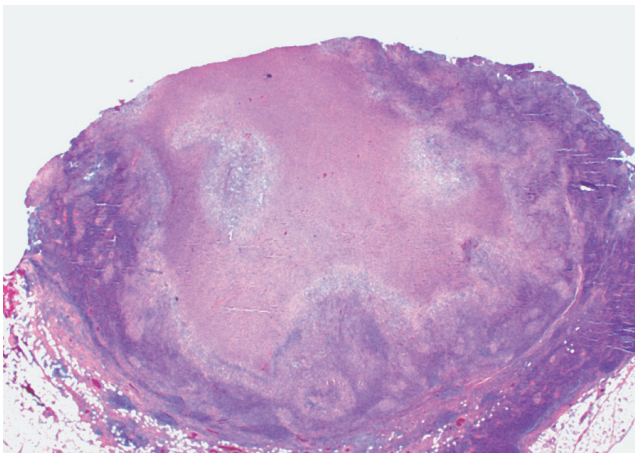

Figure 4.40
Caseating granuloma in lymph node from patient with cutaneous leishmaniasis. x8

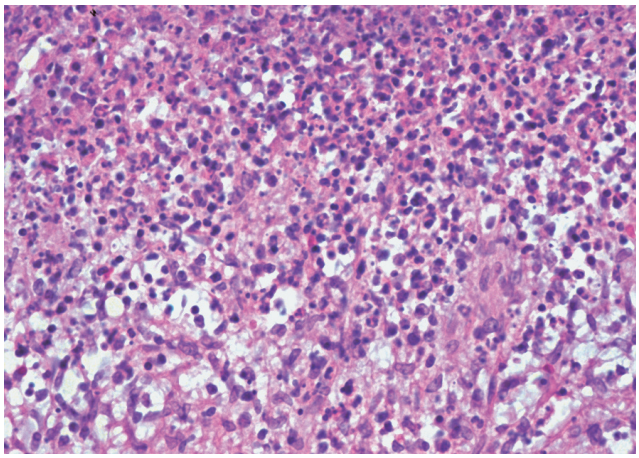

Figure 4.41
Necrotic area in lymph node from patient with cutaneous leishmaniasis. x245

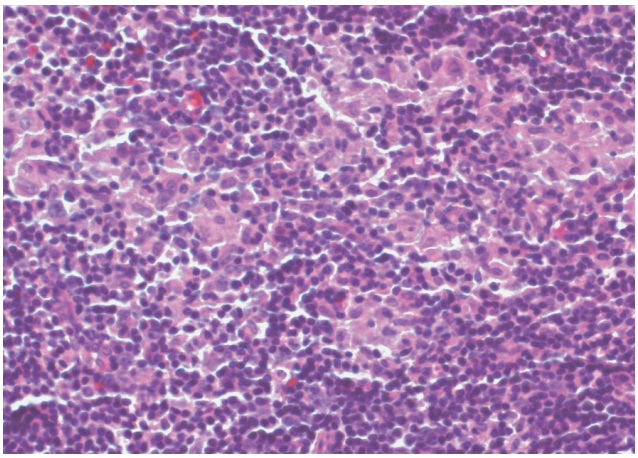

Figure 4.42
Histiocytosis in supraclavicular lymph node of 69-year-old patient from Honduras. Patient developed lymphadenopathy following cutaneous leishmaniasis on forehead. x245

stain for efficacy in diagnosis by direct smear examination.

2) **Isolation of promastigotes in in-vitro culture.** This method can be more sensitive than direct smear examination,[44,45] but some parasites, such as *L. braziliensis*, are more difficult than others to culture. Therefore, this method should be complementary to direct smear examination and should be employed whenever possible in clinically suspect cases. The lesion should be debrided to remove overlying exudate and crusting. Scrapings, aspirates, and biopsy specimens may be obtained from both the center and border of the ulcer (scrapings and aspirates are more likely to yield a positive result than tissue specimens). Increasing the number of culture attempts from the same lesion enhances the likelihood of obtaining a positive result.[45]

3) **In-vivo culture**.[46] In vivo culture (animal inoculation with a patient sample) is a sensitive diagnostic technique;

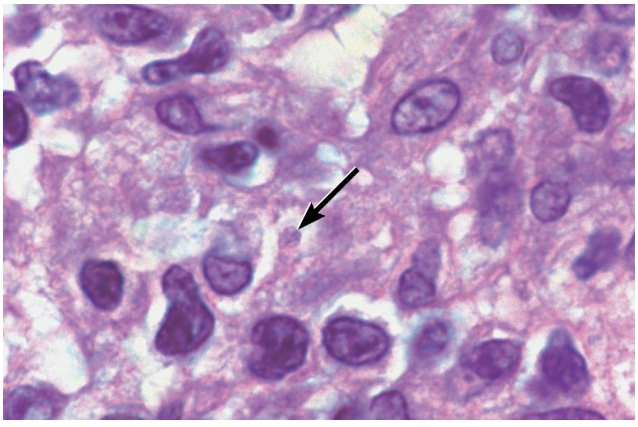

Figure 4.43
Amastigote (arrow) in lymph node of patient with cutaneous leishmaniasis. x1070

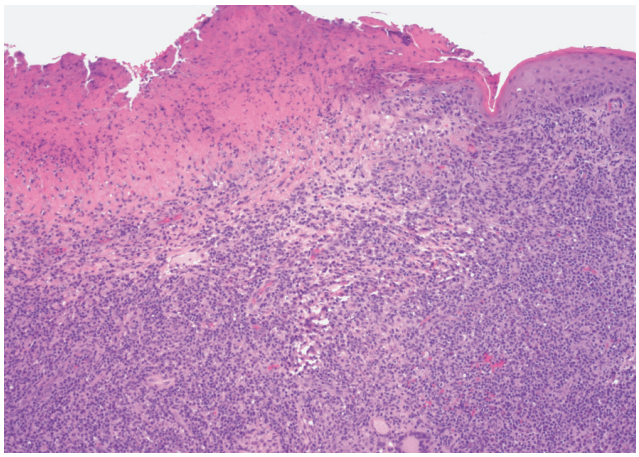

Figure 4.44
Ulceration near nares in mucosal leishmaniasis (ML). See also Figure 4.45. x63

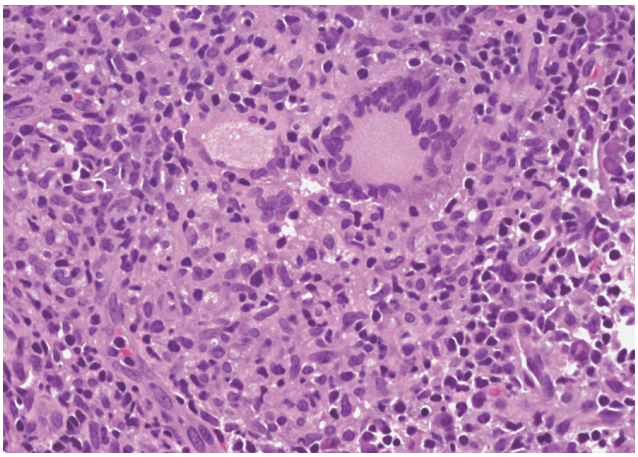

Figure 4.45
Granulomatous inflammation in same patient as Figure 4.44. x120

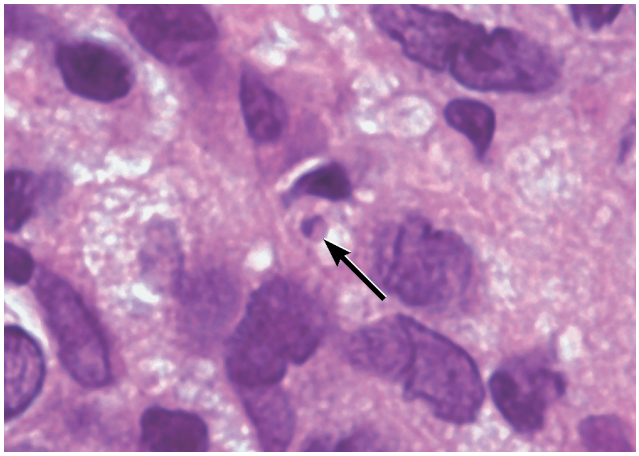

Figure 4.46
Single amastigote (arrow) in chronic mucosal leishmaniasis (ML). Note spherical nucleus and rod-shaped kinetoplast. x2000

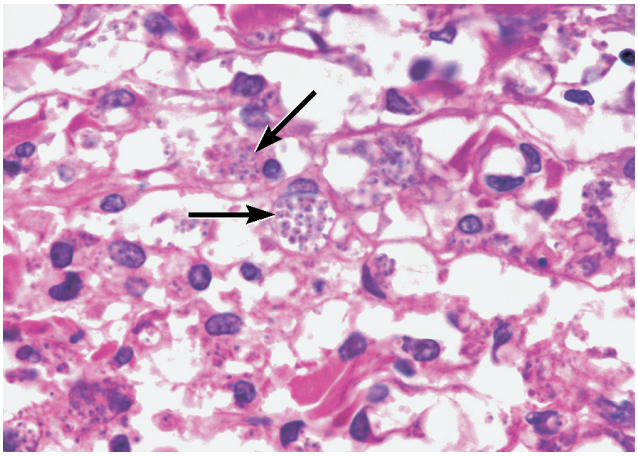

Figure 4.47
Macrophages containing multiple amastigotes (arrows) in dermis in diffuse cutaneous leishmaniasis. See also Figures 4.48 and 4.49. x430

many investigators believe a single viable amastigote can initiate infection in a susceptible animal (e.g. the golden hamster). Because the availability of appropriate laboratory animals is limited, this method should be reserved for selected cases when other tests are negative and the diagnosis is in doubt.

4) **Xenodiagnosis**. This technique involves recovering parasites from sandflies that have been allowed to feed on infected patients. Although xenodiagnosis has been used more commonly in patients with visceral leishmaniasis, xenodiagnosis has been successfully employed in cutaneous leishmaniasis, especially in oligoparasitic syndromes and with infecting parasites such as *L. braziliensis* that can be hard to recover in in vitro culture.[47]

5) **Amplification of parasite-specific DNA with polymerase chain reaction (PCR)**. There has been a dramatic proliferation of various polymerase chain reaction based molecular diagnostic tests introduced in the last decade.[48] The perfor-

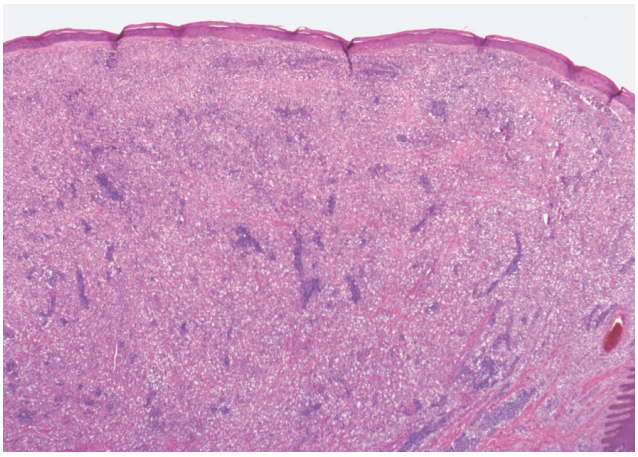

Figure 4.48
Atrophic epidermis in diffuse cutaneous leishmaniasis. Same patient as Figure 4.47. See also Figure 4.49. x17

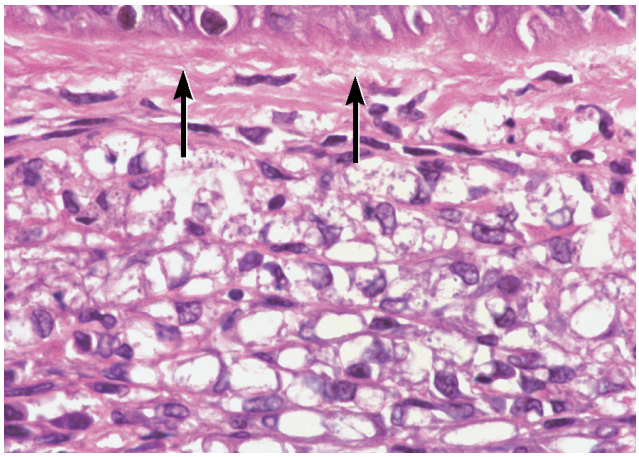

Figure 4.49
Narrow subepidermal clear zone (arrows) in diffuse cutaneous leishmaniasis (DCL). Same patient as Figures 4.47 and 4.48. x435

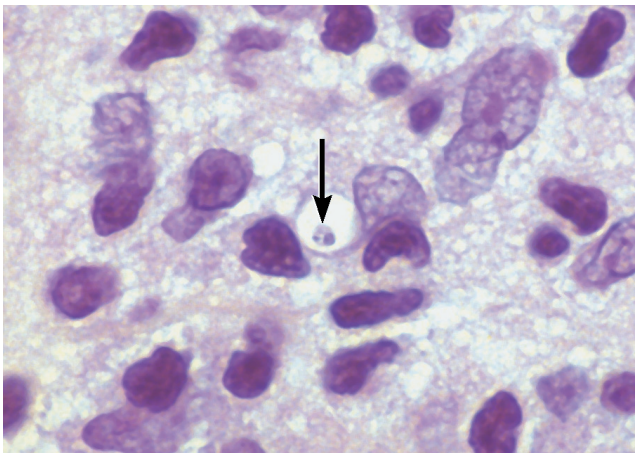

Figure 4.50
Single amastigote (arrow) in parasitophorous vacuole of histiocyte stained with H&E. Note spherical nucleus and tiny rod-shaped kinetoplast. x1500

mance characteristics vary significantly, none is commercially available, and their place in routine clinical care is not yet decided. However, locally established centers using PCR can be very useful for the confirmation of leishmaniasis in patients with oligoparasitic syndromes.

Other diagnostic methods may also be useful. In general, polyparasitic syndromes show a detectable humoral polyclonal antibody response to crude antigen, but no cellular immune response. Oligoparasitic syndromes show minimal humoral antibody response to crude antigens, but a marked cellular immune response.

There is currently no sensitive or specific serological assay for detecting *Leishmania*-specific antibody for any of the cutaneous leishmaniases. Development of an antibody-based test has been hindered by the continued use of crude promastigote-derived antigen (whole, disrupted, and solubilized preparations). Since human immune response to *Leishmania* sp is stage-specific, it is likely that amastigote-dominant or amastigote-exclusive antigens will elicit a much more specific response. Production of the antigens as recombinant proteins would allow for an epitope-dense capture antigen.

A skin-test antigen to detect DH (the Montenegro test) can also detect prior infection and corroborate the diagnosis of oligoparasitic syndromes such as ML and LR. Polyparasitic PKDL and DCL are skin test-negative (anergic to *Leishmania* antigens), while ML and LR are positive (Fig 4.57). Currently, no such test is available for use in the United States.

Treatment and Prevention

A wide variety of treatments for the cutaneous leishmaniases are employed around the world, but few of these therapies have proven consistently effective.[49-52] Recommendations based on randomized, placebo-controlled trials

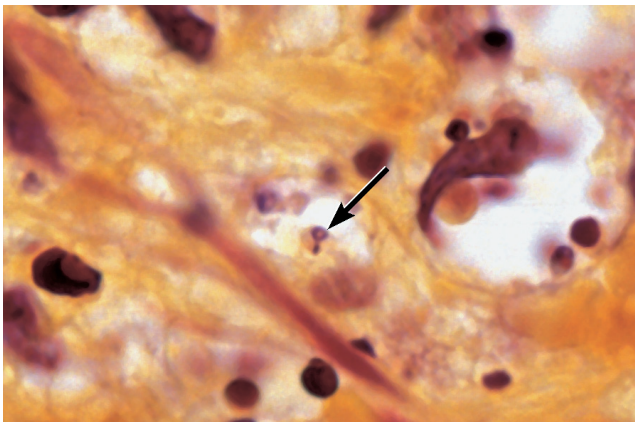

Figure 4.51
Single amastigote (arrow) stained with Brown-Hopps tissue gram stain. Note spherical nucleus and rod-shaped kinetoplast. Same patient as Figures 4.25 and 4.39. See also Figures 4.53 and 4.54. B&H x1750

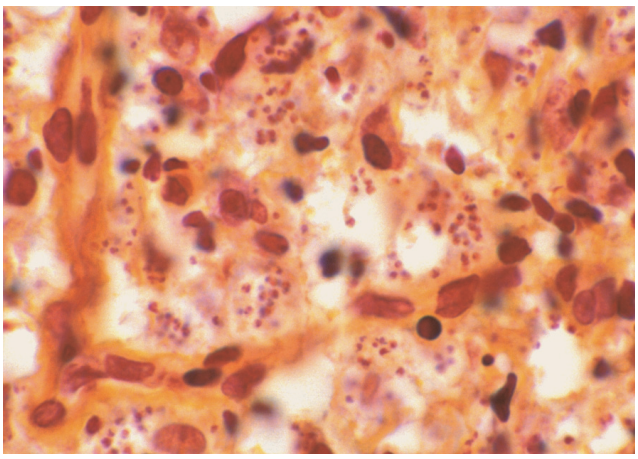

Figure 4.52
Amastigotes within histiocytes. B&H x790

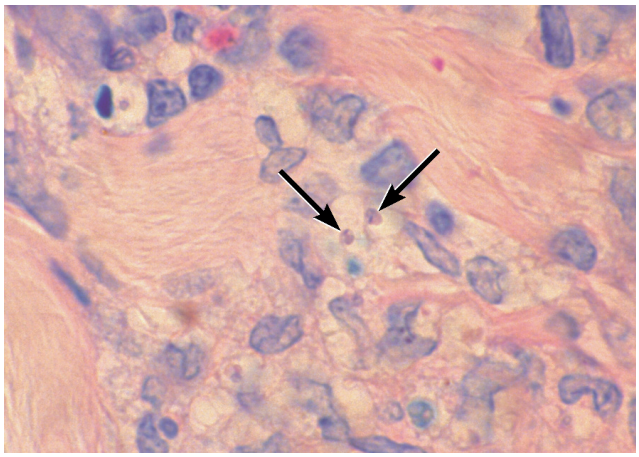

Figure 4.53
Amastigotes (arrows) visible on Giemsa-stained section. Same patient as Figures 4.25 and 4.39. See also Figures 4.51 and 4.54. Giemsa x960

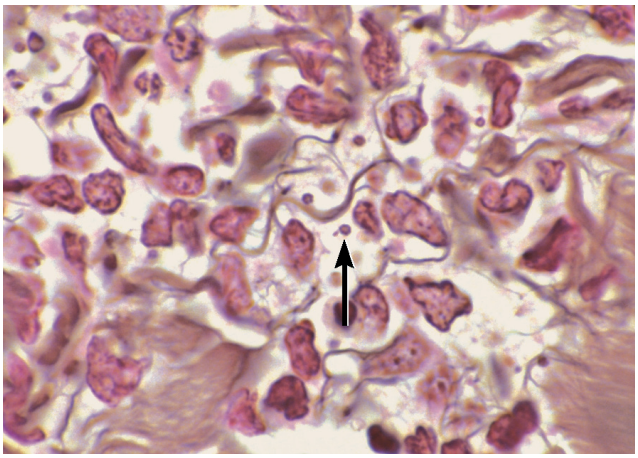

Figure 4.54
Reticulum stain demonstrating nucleus and kinetoplast of amastigote (arrow). Same patient as Figures 4.25 and 4.39. See also Figures 4.51 and 4.53. Wilder's reticulum x960

are often lacking because many treatment modalities have been evaluated in small, open-label trials with differing endpoints and insufficient follow-up to detect relapses.[53] In addition, the standard of care in many geographic areas is dictated by local traditions and patient acceptance.

Local therapies include the use of topical agents and physical modalities such as thermotherapy, cryotherapy, surgery, and electrotherapy. Physical modalities are more commonly used in the Middle East and in southwest Asia for Old World cutaneous leishmaniases. Topical use of the aminoglycoside paromomycin (aminosidine) has been extensive in the Middle East, as well as various formulations and concentrations of paromomycin and methylbenzethonium chloride in a variety of regimens.[54] In general, these formulations appear to be moderately effective against *L. major* but ineffective against *L. tropica*. These treatments have not been widely used against New World parasites. Topical antifungal agents are not effective against the cutaneous leishmaniases. Intralesional administration of pentavalent antimonials (SbV) has been used extensively in the Middle East with apparent success, but has been employed only rarely in the New World.[55]

Two SbV compounds (sodium stibogluconate (Pentostam®) and meglumine antimoniate (Glucantime®), first used in the 1940s, are still commonly used drugs for severe or complicated forms of the cutaneous leishmaniases.[2,56,57] Although there have been no clinical trials comparing treatment outcomes for these agents, most authorities consider them to be equally effective. However, systemic SbV therapy requires prolonged parenteral administration (IM or IV) of the compounds at high doses, a difficult and expensive process for health care facilities in endemic developing countries. Ulcerative and nodular CL usually respond to SbV therapy. The persistent syndromes of ML, LR, DCL,

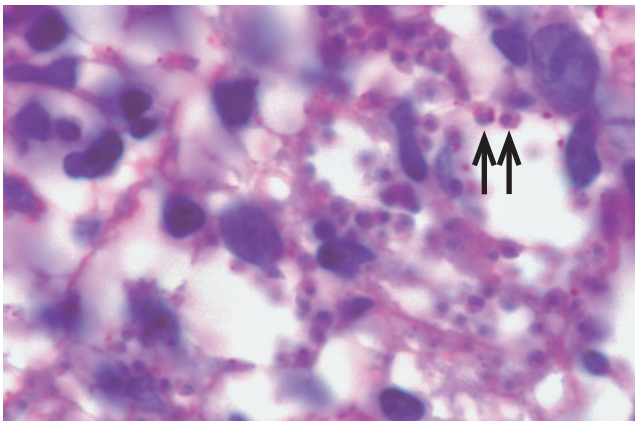

Figure 4.55
Amastigotes (arrows) visible on PAS-stained tissue section. Same patient as Figure 4.29. PAS x960

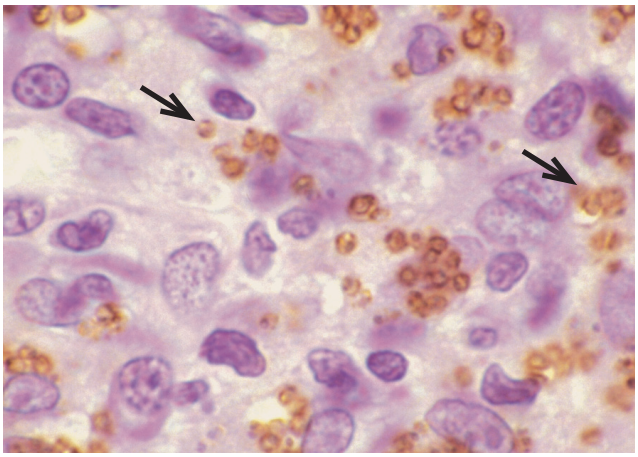

Figure 4.56
Immunoperoxidase stain demonstrating brown-stained amastigotes with darker-staining kinetoplasts (arrows). Immunoperoxidase x1140

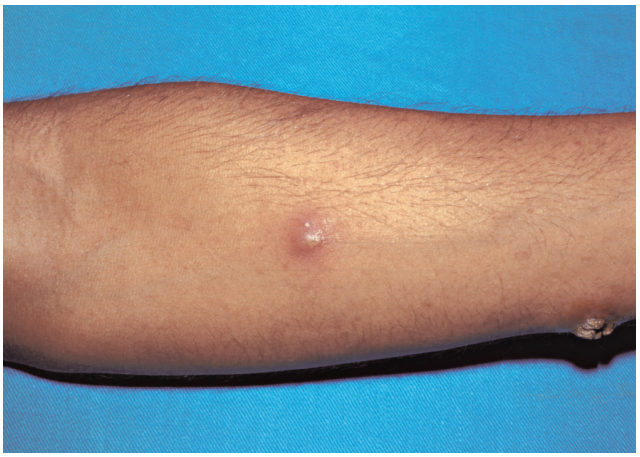

Figure 4.57
Positive Montenegro test 7 days after inoculation of leishmanin. Test is positive in oligoparasitic syndromes; negative in patients with polyparasitic disease.

and PKDL do not consistently respond to SbV or any other treatment. In patients coinfected with HIV, responses are often temporary and relapse is common.

No oral agents can be generally recommended for the treatment of any of the cutaneous syndromes. Antifungal agents such as ketoconazole, itraconazole, and fluconazole are antileishmanial in vitro and have been used in numerous uncontrolled trials and a few randomized trials in both the New World and the Old World. Itraconazole and fluconazole are only slightly more effective than placebo. Ketoconazole is modestly effective against *L. major*, *L. panamensis*, and *L. mexicana*, but ineffective against *L. tropica* and *L. braziliensis*. In Guatemala, ketoconazole has proven superior to SbV for CL caused by *L. mexicana*, but markedly inferior for CL caused by *L. braziliensis*.[58] However, it is unusual to have confirmation of the infecting species prior to the start of therapy, so it is not clear how these trial results can be implemented in routine practice.

Amphotericin B, both the deoxycholate salt and newer, less toxic liposomal preparations have been shown to be very effective treatments for many different forms of cutaneous leishmaniasis.[59-61] The cost of liposomal amphotericin B, its requirement for cold chain storage, and intravenous route of administration markedly limit the potential for beneficial impact in endemic areas but liposomal amphotericin B is now considered an acceptable first line treatment for CL in returning travelers. Early-stage ML caused by *L. braziliensis* in the New World usually responds to 20 mg/kg body weight/day of SbV administered for 20 to 40 days. Late-stage ML with extensive anatomic involvement is much less responsive.

There is no approved or effective immunoprophylaxis, chemoprophylaxis, or vaccine against infection or disease. Prevention entails protection against sandfly bites. Control measures in endemic areas are aimed at disrupting the enzootic cycle by eliminating mammalian reservoir hosts and eradicating the sandfly. Such control measures, however, are expensive, difficult to sustain, and potentially environmentally unsound.

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Figure 4.9a
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